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54 Controlled release pharmaceutical preparations.

57 Controlled release pharmaceutical preparations containing coated ion exchange resin drug complex particles, the resin particles having been treated, prior to coating, with about 15 to 25% by weight of glycerin, based on the combined weight of the glycerin and the drug resin complex particles.

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CONTROLLED RELEASE
PHARMACEUTICAL PREPARATIONS
IR-2737

The present invention relates to selective, prolonged
5 continuous release pharmaceutical preparations containing an
ion exchange resin having a pharmacologically active drug
adsorbed thereon to provide a drug resin complex, wherein at
least a portion of the resin is treated with a critical
amount of glycerin and provided with a diffusion barrier
10 coating.

BACKGROUND

U.S. Patent No. 4,221,778 discloses that controlled (i.e., selective, prolonged) continuous release of pharmacologically active drugs, under conditions such as those encountered in the gastrointestinal tract, can be achieved by the application of diffusion barrier coatings to ion exchange resin drug complex particles which have been treated, prior to coating, with an impregnating agent selected from polyethylene glycol, propylene glycol, mannitol, lactose, and methylcellulose.

BRIEF SUMMARY OF THE INVENTION

The present invention is concerned with pharmaceutical preparations comprised of ion exchange resin particles having a pharmacologically active drug adsorbed thereon to form drug-resin complex particles, the resin particles having been treated with from about 15 to about 25 percent by weight of glycerin, based on the combined weight of the glycerin and the complex particles, and thereafter coated with a water-permeable diffusion barrier coating, whereby a selective, prolonged continuous release of the drug is obtainable under conditions encountered in the gastrointestinal tract.

By varying the amount of coating, and/or by blending coated drug-resin complex with uncoated drug-resin complex, it is possible to selectively modify the preparation's drug

dissolution profile as desired.

Ion exchange resins, drugs, and coatings, and methods for preparing drug-resin complexes, for coating of the complexes, and for selectively modifying the preparation's
5 dissolution profile through blending and/or degree of coating, are disclosed and exemplified in U.S. Patent No. 4,221,778, said disclosures and examples being herein incorporated by reference.

DETAILED DESCRIPTION

.0 It has now been found that a selective, prolonged continuous release of pharmacologically active drugs, under conditions such as those encountered in the gastrointestinal tract, can be achieved by the application of diffusion barrier coatings to ion exchange resin drug complex
.5 particles, the resin particles having been treated, prior to coating, with a critical amount of glycerin, i.e., with from about 15 to about 25 percent by weight of glycerin, based on the combined weight of the glycerin and the complex (or
!0 weight of the glycerin and the resin), preferably from about 17.5 to 25 percent. As shown in Tables I and II hereinafter, treatment of the complex with 5, 10 or 30 percent glycerin, in comparison to a control using no glycerin, failed to significantly retard the dissolution
!5 rate (and in some cases even enhanced the rate), while

the use of 20 percent glycerin has been found to result in substantial retardation of the dissolution profile.

Similarly, Table III shows that treatment with from 15 to 25 percent glycerin has been found effective, with the most
5 retardation occurring with the use of from 17.5 to 25 percent.

In general, all acidic and basic drugs, especially those having short biological half-lives in the order of up to about eight hours, are potential candidates for inclusion in
10 the subject preparations. Examples are phenylpropanolamine (PPA), dextromethorphan, codeine, hydrocodone, hydralazine, ephedrine, pseudoephedrine, verapamil, theophylline, ibuprofen, and para-amino salicylic acid. PPA, a
sympathomimetic amine drug with a biological half life of
15 3.9 hours in man and a pKa of 9.4 was chosen as a model drug for use in these illustrative examples. The loading of the drug on the resin particles can be from about 1 to about 90 percent by weight, although 15 to 50 percent is the normal practical range.

20 Similarly, a wide range of cationic (for the basic drugs) or anionic (for the acidic drugs) exchange resins can be used to form the drug resin complex, in particle sizes normally ranging from about 75 to 1000 μm . The illustrative examples employ Amberlite IRP-69 resin, a cationic exchange
25 resin consisting of 100-200 mesh (75-150 μm) fractured resin particles of Amberlite IR-120. The parent resin of

Amberlite IR-120 and Amberlite IRP-69 is described by the manufacturer as gel-type divinylbenzene sulfonic acid cation exchange resin which swells in water with a pH range of 0-14. Other suitable ion exchange resin candidates include
5 synthetic ion exchange resins with different polymeric matrices (e.g. methacrylic, acrylic, phenol formaldehyde), ion exchange agents with cellulosic or dextran polymer matrices, and inorganic ion exchange matrices. The resins should not have inherent pharmacological or toxic properties.

10 Adsorption of the drug onto the ion exchange resin particles to form the drug resin complex is a well known technique as shown in U.S. Patent Nos. 2,990,332 and 4,221,778. In general the drug is mixed with an aqueous suspension of the resin and the complex is then washed and
15 dried. Adsorption of drug onto the resin may be detected by a change in the pH of the reaction medium.

As shown by the illustrative examples below, such resin drug complexes rapidly release the drug in 0.1 normal hydrochloric acid (0.1N HCl) dissolution medium (which
20 simulates the fluids of the gastrointestinal tract), e.g., an uncoated and untreated Amberlite IRP-69 phenylpropanolamine complex with a 22.5% drug loading released 86.3% of the drug in 1 hour (Control A). Some retardation of this rapid release can be obtained by
25 attempting to coat the complex particles, without glycerin pretreatment, with a diffusion barrier coating, e.g.,

Control B shows that at an 11.1% (applied) coating level 62.8% of the drug was released in 1 hour. It has now been discovered that the efficiency of the coating on the complex particles can be improved and the release of the drug

5 further slowed by treating the resin particles prior to coating with about 15-25% glycerin, resulting in the ability to selectively prolong the release of drugs from drug-resin complexes. For example, as shown in Example 1 (Table I), pretreatment of the complex particles with 20% glycerin and

10 use of an 11.1% coating level resulted in only 49.1% of the drug being released in 1 hour. While the glycerin is normally applied to the drug-resin complex, it may be applied to the resin prior to complexing, as in the case where the resin particles are coated prior to complexing

15 with the drug.

The water-permeable, diffusion barrier coating material can in general be any of the conventional synthetic or natural film-forming materials with diffusion barrier properties and with no inherent pharmacological or toxic

20 properties. Ethylcellulose, a water insoluble film-forming agent was used as the model diffusion barrier membrane material in the illustrative examples. A plasticizer, Durkex 500 vegetable oil, was used to improve the film-forming characteristics of ethylcellulose. The amount

25 of coating used depends on the degree of drug release prolongation desired.

Conventional coating solvents (such as ethanol, or a methylene chloride/acetone mixture, or coating emulsions) and coating procedures can be employed to coat the particles. In the illustrative examples, coatings were carried out by using a Wurster coating apparatus. Techniques of fluid bed spray coating are taught, for example, in U.S. Patent Nos. 3,089,824; 3,117,027; and 3,253,944. The coating is normally applied to the drug resin complex, but alternatively can be applied to the resin before complexing with the drug.

Dissolution data in the following examples demonstrate that the controlled, continuous release of drugs from drug resin complex particles is now obtainable by use of critical amounts of glycerin and of diffusion barrier coatings, and that the dissolution profiles of such complexes are relatively unaffected by conditions encountered in the gastrointestinal tract.

Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired. In addition to oral administration, the preparations of the subject invention are also suitable for topical, rectal or vaginal administration in dosages varying over a wide range, for example, from about 0.1 to about 1000 mg, depending on the nature of the drug and its intended usage. The compositions can take the form of tablets, powders,

capsules, liquid suspensions or other conventional dosage forms.

ILLUSTRATIVE EXAMPLES

The following dissolution test apparatus and procedures
5 were used in the examples to simulate conditions encountered
in the gastrointestinal tract: Five hundred ml of the
dissolution medium (0.1N HCl) was placed in a round bottom
flask immersed in a suitable water bath and the temperature
allowed to rise to $37^{\circ}\pm 0.5^{\circ}\text{C}$. The flask was equipped with a
10 paddle which was agitated at 100 rpm. The dissolution
medium was pumped from the vessel through a cotton filter.
Polyethylene tubing carried the filtered media via a
peristaltic pump through a 1 cm flow cell of a Beckman model
35 recording spectrophotometer (equipped with a cell
15 changer) and returned it to the vessel. The flow rate was
adjusted to 16 ml/minute. In this way, each of the six
vessels and a standard could be monitored at 15 minutes or
other suitable intervals. The spectrophotometer was
operated at 257 nm in a single beam mode to monitor six
20 resin complex samples and one PPA hydrochloride standard.
Each dissolution vessel contained resin complex sample
equivalent to 90.6 mg of PPA base. The standard PPA
solution contained 90.6 mg of PPA base in 500 ml of 0.1 N
HCl. Microscopic examinations of particles of resin were
25 carried out using a Bausch and Lomb low power binocular

microscope (objective X3 and eyepiece X10). Diffusion barrier coatings were carried out using an air suspension coating technique employing a Wurster coating apparatus (such as made by Aeromatic U.S. Inc., Glatt Air Techniques, Inc., and Dairy Equipment Corp.).

TEST SERIES I

Control A below illustrates the effect of omitting both the glycerin treatment and the diffusion barrier coating, while Control B illustrates the effect of omitting pretreatment of the drug resin complex prior to coating. Comparative Examples 1A, 1B, and 1C illustrate the use of levels of glycerin outside of the critical range disclosed herein.

CONTROL A

Preparation of Uncoated PPA Resin Complex (26% theoretical load):

PPA Hydrochloride	32.28 kg
Amberlite IRP-69 Resin	74.88 kg
Purified Water	324 liters

The Amberlite IRP-69 resin was suspended in 324 liters of purified water in a 100 gallon lined kettle provided with a suitable stirrer. The PPA hydrochloride was then added to the stirring resin slurry. The mixing was continued for two hours. The resin slurry was then transferred to a suitable

centrifuge and the resin separated from the aqueous medium. The resin core was then washed with purified water till free of chloride ions. The resin core was then fluid-bed dried to an exit air temperature of 45°C and to a moisture of
5 5-10%. The dried resin complex was found to contain 22.54% PPA. The average particle size was 96 µm.

The dissolution results obtained on this uncoated resin complex are reported in Table I and show very rapid drug release.

10 CONTROL B

Preparation of Coated, Untreated, PPA Resin Complex

The above PPA resin complex was coated in two separate runs as follows, without any glycerin pretreatment, at 11.1% coating:

15 (a) Seven hundred g of PPA resin complex (Control A) was used as the core material. One thousand one hundred and sixty-seven ml of a coating solution of the following composition was quantitatively applied to the particles:

20 Ethylcellulose (50 cps)	62.5 g
Durkex 500 refined vegetable oil	25.0 g
Acetone	116.7 ml
Methylene chloride qs	1167.0 ml

The coating is expressed as the percent by weight of the non-volatile coating solids applied (ethylcellulose and
25 Durkex 500), based on the total non-volatile solids (coating

applied plus complex). The coating of the core particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 20 mls/minute (total time 58 minutes). The inlet air temperature was about 42°C. The outlet air
5 temperature range was 23-29°C. The average size of the coated particle was 102 μ m. The coated particles assayed 20.27% for PPA.

(b) Six hundred g of PPA resin complex (control A) was used as the core material. One thousand ml of a coating
10 solution proportioned as in run (a) was quantitatively applied to the particles. The coating of the core particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 7.1 ml/minute (total time 140 minutes). The inlet air temperature was about 42°C. The outlet air
15 temperature was about 23°C. The average size of the coated particle was 97 μ m. The coated particles assayed 19.0% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table I and show some retardation of
20 drug release.

EXAMPLE I

The PPA resin complex of Control A was treated with glycerin at a 20% level as follows:

25	PPA Resin Complex	680 g
	Glycerin	170 g
	Purified water	275 ml

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and added to the resin complex. They were then mixed for 10 minutes and fluid-bed dried to a moisture content of 5%.

5 The dried treated resin complex was screened through 60 mesh stainless steel screen.

Five hundred and fifty g of the resin complex was used as the core material for applying coating at an 11.1% level. Nine hundred and fifteen ml of a coating solution as
10 in control B was quantitatively applied to the particles. The coating of the particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 12.4 ml/minute (total time 74 minutes). The inlet air temperature range was 42-44°C. The outlet air temperature range was
15 22-24°C. The average size of the coated particle was 107 µm. The coated particles assayed 17.06% for PPA.

The dissolution results are reported in Table I and show significant retardation compared to the controls and to the following comparative examples at 5, 10 and 30% glycerin
20 treatment levels.

COMPARATIVE EXAMPLES 1A, 1B, and 1C

In three separate runs (1A, 1B, and 1C) the PPA resin complex of Control A was impregnated with glycerin at levels of 5%, 10% and 30%, respectively, following the procedure of
25 Example 1. Each treated complex was then coated at a level

of 11.1% using a coating solution as described in Control B, the coating being carried out in a 6-inch fluid-bed coating apparatus.

The coatings for runs 1A, 1B, and 1C were done at rates of 15.4, 15.9, and 14.5 ml/minute (for total coating times of 65, 63, and 69 minutes, respectively). The air inlet temperature was about 41°C in each instance. The outlet air temperatures were 24-27°C, 26-28°C, and 28-29°C, respectively. The average size of the coated particles was 103, 98, and 133 μ m. The coated particles assayed for 18.3%, 18.3% and 14.4% PPA.

The dissolution data are reported in Table I and are not significantly different from Control B (no glycerin pretreatment).

5

Table I

%PPA Released at:						
<u>Example</u>	<u>0.25 hr</u>	<u>0.5 hr</u>	<u>1 hr</u>	<u>2 hr</u>	<u>3 hr</u>	
Control A	86.6	86.2	86.3	87.3	88.1	
Control B	47.7	56.8	66.2	72.0	75.2	
0 Example 1	37.1	43.0	49.1	55.3	58.4	
Comp. Ex. 1A	46.8	55.1	63.1	69.6	72.7	
Comp. Ex. 1B	48.8	57.8	63.8	69.6	71.8	
Comp. Ex. 1C	55.9	63.0	69.2	74.2	77.4	

Uncoated complex particles (as in Control A) and coated complex particles (as in Example 1) can be mixed so as to match a variety of desired dissolution profiles.

TEST SERIES II

5 The dissolution results of Control A (the uncoated PPA resin complex) are repeated in Table II. The remaining tests substantially correspond to those of Test Series I except that a 16% coating level is used. The percent glycerin used in Control C, Example 2, and Comparative
10 Examples 2A and 2B is 0%, 20%, 10%, and 30%, respectively.

CONTROL C

Preparation of Coated, Untreated, PPA Resin Complex

The PPA resin complex of Control A was coated in two separate runs as follows, without any glycerin
15 pretreatment, at a 16% coating level:

(a) Five hundred and fifty g. of PPA resin complex (Control A) was used as the core material. One thousand four hundred ml of a coating solution of the following composition was quantitatively applied to the particles.

20 Ethylcellulose (50 cps)	75.0 g .
Durkex 500 refined vegetable oil	30.0 g
Acetone	140.0 ml
Methylene chloride qs	1400.0 ml

The coating of the particles was carried out in a 6-inch
25 fluid-bed coating apparatus at the rate of 15.7 ml/minute

(total coating time 89 minutes). The inlet air temperature range was 41-42°C. The outlet air temperature range was 24-26°C. The average size of the coated particle was 103 μm . The coated particles assayed 19.1% for PPA.

- 5 (b) Run (a) was repeated except that the coating was carried out at the rate of 13.7 ml/minute (total coating time 102 minutes). The inlet air temperature range was 41-59°C. The outlet air temperature range was 20-23°C. The average size of the coated particle was 88 μm . The coated particles assayed 18.6% for PPA.
- 10

The mean value of the dissolution results from runs (a) and (b) are reported in Table II.

EXAMPLE 2

- The PPA resin complex core of Example 1 (PPA resin complex treated with glycerin at 20% level) was coated in two separate runs at a 16% coating level as follows:
- 15

- (a) Five hundred and fifty g of the resin complex of Example 1 was used as the core material. One thousand four hundred ml of a coating of the composition in Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 15.2 ml/minute (total coating time 92 minutes). The inlet temperature range was 41-42°C. The outlet temperature range was 21-22°C. The average size
- 20

of the coated particle was 127 μm . The coated particles assayed at 16.6% for PPA.

(b) Run (a) was repeated except that the coating was carried out at the rate of 14.6 ml/minute (total coating
5 time 96 minutes). The inlet temperature range was 42-56°C. The outlet temperature range was 20-24°C. The average size of the coated particle was 98 μm . The coated particles assayed 15.8% for PPA.

The mean values of the dissolution results from runs
10 (a) and (b) are reported in Table II and show significant retardation compared to Controls A and C and to the following comparative examples at 10 and 30% glycerin treatment levels.

COMPARATIVE EXAMPLE 2A

15 The PPA resin complex core of Comparative Example 1B (PPA resin complex impregnated with glycerin at 10% level) was coated at a 16% coating level as follows:

Five hundred and fifty g of the resin complex was used as the core material. One thousand four hundred ml of a
20 coating solution of the composition in control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 13.3 ml/minute (total coating time 105 minutes). The inlet air temperature range was
25 41-43°C. The outlet air temperature range was 26-31°C.

The average size of the coated particle was 100 μm . The coated particles assayed 18.3% for PPA.

The dissolution data are reported in Table II and are not significantly different from Control C (with no glycerin pretreatment).

COMPARATIVE EXAMPLE 2B

The PPA resin complex core of Comparative Example 1C (PPA resin complex impregnated with glycerin at 30% level) was coated at a 16% coating level as follows:

Five hundred and fifty grams of the resin complex was used as the core material. One thousand four hundred ml of a coating of the composition in Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6-inch fluid-bed coating apparatus at the rate of 10.8 ml/minute (total coating time 130 minutes).

The inlet temperature range was 41-49°C. The outlet temperature range was 24-29°C. The average particle size of the coated particle was 177 μm . The coated particle assayed 14.1% for PPA.

The dissolution data are reported in Table II. As with Comparative Example 2A, the dissolution rate has actually been enhanced (relative to Control C) rather than achieving the desired retardation.

Table II

		% PPA Released at:				
<u>Example:</u>		<u>0.25 hr</u>	<u>0.5 hr</u>	<u>1 hr</u>	<u>2 hr</u>	<u>3 hr</u>
	Control A	86.6	86.2	86.3	87.3	88.1
5	Control C	35.2	43.9	52.2	59.2	62.4
	Example 2	26.3	31.8	38.1	44.1	47.6
	Comp. Ex. 2A	39.3	48.5	55.6	62.8	65.6
	Comp. Ex. 2B	52.3	59.3	64.4	70.3	73.5

TEST SERIES III

10 The following tests illustrate that glycerin is effective at a 15 to 25% level, particularly at 17.5 to 25%. A 16% coating level is used as in Test Series II. Control D is uncoated and untreated (with glycerin), while Control E is coated but untreated.

15 CONTROL D

Preparation of Uncoated, Untreated, PPA Resin Complex:

PPA Hydrochloride	135 kg
Amberlite XE-69	319.2 kg
Purified Water	1010 liters

20 A PPA resin complex was prepared according to the general procedure of Control A, except that the complex was dried at 52-57°C in a drying oven to a moisture less than 5%. The dried complex was found to contain 26.10% PPA. The average particle size was 78 µm.

The dissolution results are reported in Table III and show very rapid drug release.

CONTROL E

Preparation of Coated, Untreated, PPA Resin Complex

5 The PPA Resin Complex of Control D was coated in two separate runs as follows, without any glycerin pretreatment, at 16.0% coating:

 (a) Five hundred fifty g of PPA resin complex of Control D was used as the core material. One thousand four
10 hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the core particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.9 mls/minute (total time 83 minutes). The inlet air temperature range
15 was 32-35°C. The outlet air temperature range was 21-23°C. The average size of the coated particle was 96 μ m. The coated particles assayed 21.44% for PPA.

 (b) Five hundred fifty g of PPA resin complex of Control D was used as the core material. One thousand four
20 hundred ml of a coating solution as in run (a) was quantitatively applied to the particles. The coating of the core particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 17.3 mls/minute (total time 81 minutes). The inlet air temperature range was 32-36°C.
25 The outlet air temperature range was 22-24°C. The average

size of the coated particle was 105 μm . The coated particles assayed 21.76% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table III and show some retardation
5 of drug release.

EXAMPLE 3

The PPA resin complex of Control D was treated with glycerin at a 15% level and coated in two separate runs as follows:

10	PPA resin complex	1,020.0 g
	Glycerin	180.0 g
	Purified water	400.0 ml

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and
15 added to the resin complex. This was then mixed for 15 minutes and fluid-bed dried to a moisture content of 5%. The dried treated resin complex was screened through a 60 mesh stainless steel screen.

(a) Five hundred fifty g of the above impregnated resin
20 complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.3 ml/minute
25 (total coating time 86 minutes). The inlet air temperature range was 32-33°C. The outlet air temperature range was

22-23°C. The average size of the coated particle was 96 μ m. The coated particles assayed 18.90% for PPA.

(b) Five hundred fifty g of the above impregnated resin complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.7 ml/minute (total coating time 84 minutes). The inlet air temperature range was 32-37°C. The outlet air temperature range was 20-22°C. The average size of the coated particle was 90 μ m. The coated particles assayed 17.98% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table III and show substantial retardation in dissolution relative to Control E, although not to the same degree as shown in Examples 4-7.

EXAMPLE 4

The PPA resin complex of Control D was treated with glycerin at a 17.5% level and coated in two separate runs as follows:

PPA resin complex	990.0 g
Glycerin	210.0 g
Purified water	400.0 g

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and added to the resin complex. This was then mixed for 15

minutes and fluid-bed dried to a moisture content of 5%. The dried treated resin complex was screened through a 60 mesh stainless steel screen.

(a) Five hundred fifty g of the above impregnated resin
5 complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.5 ml/minute (total
10 coating time 85 minutes). The inlet air temperature was 32°C. The outlet air temperature range was 21-23°C. The average size of the coated particle was 94 μ m. The coated particles assayed 17.98% for PPA.

(b) Five hundred fifty g of the above impregnated resin
15 complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.3 ml/minute
20 (total coating time 86 minutes). The inlet air temperature range was 32-36°C. The outlet air temperature range was 20-23°C. The average size of the coated particle was 86 μ m. The coated particles assayed 18.60% for PPA.

The mean value of the dissolution results from runs (a)
25 and (b) are reported in Table III and show significant retardation in dissolution compared to those of Control E.

EXAMPLE 5

The PPA resin complex of Control D was treated with glycerin at a 20.0% level and coated in two separate runs as follows:

5	PPA resin complex	1,040.0 g
	Glycerin	260.0 g
	Purified water	440.0 ml

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and
0 added to the resin complex. This was then mixed for 15 minutes and fluid-bed dried to a moisture content of 5%. The dried treated resin complex was screened through a 60 mesh stainless steel screen.

(a) Five hundred fifty g of the above impregnated resin
5 complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 17.1 ml/minute
0 (total coating time 82 minutes). The inlet air temperature range was 32-38°C. The outlet air temperature range was 21-24°C. The average size of the coated particle was 94 µm. The coated particles assayed 18.64% for PPA.

(b) Five hundred fifty g of the above impregnated resin
5 complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The

coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 17.5 ml/minute (total coating time 80 minutes). The inlet air temperature range was 32-36°C. The outlet air temperature range was 22-24°C. The average size of the coated particle was 122 μ m. The coated particles assayed 17.56% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table III and show significant retardation in dissolution compared to those of Control E.

10 EXAMPLE 6

The PPA resin complex of Control D was treated with glycerin at a 22.5% level and coated in two separate runs as follows:

15	PPA resin complex	930.0 g
	Glycerin	270.0 g
	Purified water	400.0 ml

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and added to the resin complex. This was then mixed for 15 minutes and fluid-bed dried to a moisture content of 5%. The dried treated resin complex was screened through a 60 mesh stainless steel screen.

(a) Five hundred fifty g of the above impregnated resin complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The

coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.5 ml/minute (total coating time 85 minutes). The inlet air temperature range was 32-33°C. The outlet air temperature range was 21-23°C. The average size of the coated particles was 82 μm . The coated particles assayed 16.70% for PPA.

(b) Five hundred fifty g of the above impregnated resin complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.9 ml/minute (total coating time 83 minutes). The inlet air temperature range was 32-33°C. The outlet air temperature range was 19-23°C. The average size of the coated particle was 96 μm . The coated particles assayed 16.20% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table III and show significant retardation in dissolution compared to those of Control E.

EXAMPLE 7

The PPA resin complex of Control D was treated with glycerin at a 25.0% level and coated in two separate runs as follows:

PPA resin complex	900.0 g
Glycerin	300.0 g
Purified water	400.0 ml

The PPA resin complex was taken in a suitable planetary mixer. The glycerin was dissolved in the purified water and added to the resin complex. This was then mixed for 15 minutes and fluid-bed dried to a moisture content of 5%.

- 5 The dried treated resin complex was screened through a 60 mesh stainless steel screen.

- (a) Five hundred fifty g of the above impregnated resin complex was used as the core material. One thousand four hundred ml of a coating solution of the composition of
- 10 Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 16.9 ml/minute (total coating time 83 minutes). The inlet air temperature range was 32-37°C. The outlet air temperature range was
- 15 20-23°C. The average size of the coated particle was 108 μm . The coated particles assayed 16.50% for PPA.

- (b) Five hundred fifty g of the above impregnated resin complex was used as the core material. One thousand four hundred ml of the coating solution of the composition of
- 20 Control C was quantitatively applied to the particles. The coating of the particles was carried out in a 6 inch fluid-bed coating apparatus at the rate of 15.7 ml/minute (total coating time 89 minutes). The inlet air temperature range was 32-37°C. The outlet air temperature range was
- 25 21-23°C. The average size of the coated particle was 100 μm . The coated particles assayed 16.38% for PPA.

The mean value of the dissolution results from runs (a) and (b) are reported in Table III and show significant retardation in dissolution compared to those of Control E.

Table III

5	<u>Example</u>	% PPA Released at:				
		<u>0.25 hr</u>	<u>0.5 hr</u>	<u>1 hr</u>	<u>2 hr</u>	<u>3 hr</u>
	Control D	81.7	81.3	81.6	82.6	82.7
	Control E	40.2	53.0	64.9	75.0	81.3
	Example 3	42.5	50.7	59.1	68.8	73.9
10	Example 4	41.4	47.6	53.7	59.5	62.8
	Example 5	36.6	44.1	51.6	59.2	63.6
	Example 6	41.5	48.6	54.9	58.3	63.6
	Example 7	41.6	46.7	53.3	59.4	62.7

Applying the foregoing discovery, controlled release dosage forms can be formulated for human or veterinary use to contain suitable mixtures of coated and uncoated complex particles such that a desired controlled release profile of the drug is obtained. The dosage forms can be solid (such as powders, capsules and tablets) or liquid (such as a suspension of complex particles in a palatable vehicle).

WHAT IS CLAIMED IS:

1. A pharmaceutical preparation comprising ion
exchange resin particles having a pharmacologically active
drug adsorbed thereon to form drug-resin complex particles,
5 which resin particles have been treated with from about 15 to
about 25 percent by weight of glycerin, based on the combined
weight of the glycerin and the complex particles, and
subsequently coated with a water-permeable diffusion barrier.
2. A pharmaceutical preparation as in Claim 1
10 wherein the resin particles have been treated with from
about 17.5 to about 25 percent by weight of glycerin.
3. A pharmaceutical preparation as in Claim 2
wherein the drug is phenylpropanolamine.
4. A pharmaceutical preparation as in Claim 2 wherein
15 the coating is comprised of ethyl cellulose.

Claims for the Contracting State AT

1. A process for preparing a pharmaceutical preparation in which a pharmaceutically active drug is adsorbed on particles of an ion exchange resin to form drug-resin complex particles, and the complex particles are provided with a water-permeable diffusion barrier coating, characterized by treating the resin particles, prior to coating, with from about 15 to about 25 percent by weight of glycerin, based on the combined weight of the glycerin and the complex particles.

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2. The process of claim 1 wherein the resin particles have been treated with from about 17.5 to about 25 percent by weight of glycerin.

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3. The process as in claim 2 wherein the drug is phenylpropanolamine.

4. The process as in claim 2 wherein the coating is comprised of ethyl cellulose.

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(17)

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(54) **Controlled release pharmaceutical preparations.**

(57) **Controlled release pharmaceutical preparations containing coated ion exchange resin drug complex particles, the resin particles having been treated, prior to coating, with about 15 to 25% by weight of glycerin, based on the combined weight of the glycerin and the drug resin complex particles.**



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EUROPEAN SEARCH REPORT

0171528

Application number

EP 85 10 6695

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X, D	US-A-4 221 778 (Y. RAGHUNATHAN) * Whole document *	1-4	A 61 K 9/18 A 61 K 9/52
Y	DE-B-2 246 037 (TAESCHNER & CO.) * Example 1a; page 5, lines 10-18; claims *	1, 2	
D, Y	US-A-2 990 332 (J.W. KEATING) * Examples 22, 25; claims *	1, 2	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K 9/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 23-01-1986	Examiner BERTE M.J.
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